



## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN-RE APPLICATION OF: YAMAZAKI, *et al.*

EXAMINER: FOSTER, CHRISTINE E.

APPLICATION NO.: 10/661,790

ART UNIT: 1641

FILED: September 11, 2003

CONF. NO: 9161

FOR: MEMBRANE BASED ASSAYS**Pre-Appeal Brief Request for Review**

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Sir:

This Pre-Appeal Brief Request for Review responds to the Advisory Action dated July 10, 2007, in which the Examiner maintained rejection of the claims and refused consideration of Applicants' remarks presented in the response after final rejection, filed July 3, 2007. This request is accompanied by a Notice of Appeal, and contains no amendments, affidavits or other evidence.

Accordingly, Applicants request review of the outstanding rejections prior to filing an Appeal Brief in the present application on the grounds that the rejection is based on legal error.

I. The Pending Claims

Claims 1-7, 10, 34-36, 40, and 42-43 are pending and are set forth in the listing of claims in Applicants' response filed July 3, 2007, beginning on page 2. Claims 8-9, 11-33, 37-39 and 41 are canceled.

II. Rejections Under 35 U.S.C. §112, First Paragraph

The pending claims stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to satisfy both the written description requirement and the enablement requirement. The two rejections are addressed in turn.

A. Written Description Rejection

At issue is whether the claimed assay is described in the specification in such a way as to reasonably convey to a skilled artisan that the inventors had possession of the claimed assay. In particular, it is the Examiner's position that the specification fails to provide written description of the claimed genera of test agents and lipid bilayer-associated components (Final Office action dated

May 3, 2007; paragraph bridging pages 3-4). The Examiner maintains that a skilled person "would not envisage possession of methods involving any type of test agent and any type of lipid-bilayer associated component based on the single example of cholera toxin binding to GM1, given that the specification makes particular mention of the large size and multivalent binding capacity of cholera toxin, and in the absence of evidence to show that all test agents, upon binding to a lipid-bilayer associated component, would possess the claimed functional characteristics of being able to produce detectable changes in membrane fluidity" (Final Office action dated May 3, 2007; first paragraph on page 11).

#### A1. The Legal Standard

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. M.P.E.P. § 2163. Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in the detailed drawings or in structural chemical formulas [...]. M.P.E.P. §2163. The description needed to satisfy the requirements of 35 U.S.C 112 varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. M.P.E.P. §2163, citing to *Capon v. Eshhar*, 418 F.3d 1357 (Fed. Cir. 2005)).

#### A2. Meeting the Legal Standard

The rejection is based on the Examiner's position that a skilled person "would not envisage possession of methods involving any type of test agent and any type of lipid-bilayer associated component based on the single example of cholera toxin binding to GM1". With respect to disclosure related to lipid-bilayer associated components, Applicants direct the panel to the following disclosure in the application as filed:

Page 6, lines 26-31, where a definition is given of "lipid-bilayer associated component", as referring to any component comprising a lipid bilayer expanse, including e.g., lipids, glycolipids, sterols, lipid-linked molecules, fatty acids, proteins, nucleic acids, etc.

Page 11, lines 9-30, where exemplary vesicle-forming lipids are set forth, including structural details of such lipids;

Page 13, lines 1-9, where various biomolecules for incorporation into a bilayer lipid expanse are described;

Page 21, lines 17-19, where membrane associated components are described as including glycolipids, fatty acids, sterols;

Page 21, Example 2, where a working example using the lipid ganglioside GM1 is set forth;

Page 30, lines 17-23, where mycolic acid is described as a lipid-based component for interaction with an antibiotic;

Page 30, lines 23--23, where ergosterol is described as a lipid-based component for interaction with an antibiotic;

Page 32, in Example 5, where a working example using an endotoxin component (lipopolysaccharide) in admixture with a lipid, is described.

With respect to disclosure related to a test agent, Applicants direct the panel to the following disclosure in the application as filed:

Page 1 lines 13-30, where the evaluation of potentially active compounds, or "test agents", for interaction with a membrane protein is described;

Page 3, lines 6-22, where the test agents are described as including small molecules, polypeptides, antibodies, biomolecules, polyenes, lipopeptides, cationic peptides, etc.

Page 21, Example 2, where a working example using the cholera toxin subunit B as a test agent is set forth.

Page 30, lines 15-23, where antibiotics as a test agent are described, with specific mention of isoniazid and pyridoxine;

Page 30, lines 24-26, where the drugs fluconazole and ketoconazole as antifungal drugs are described as test agents, for interaction with the lipid ergosterol;

Page 33, lines 9-10, in Example 5, where a combinatorial peptide library and a chemical library are described as the test agent.

Page 33, lines 15-18, in Example 5, where compounds in a chemical library are described as being, for example, polyenes, lipopeptides, cationic peptides.

Applicants submit that the application as originally filed meets the legal standard required to establish that the inventors had possession of the claimed assay at the time of filing, in view of (i) the description of various and specific bilayer-associated components and test agents and (ii) an actual working example (Example 2) of a lipid-bilayer associated components and a test agent.

**A3. Consideration of Examiner's Remarks**

**A3.1** The Examiner states that there is no disclosure of the claimed genera of test agents and lipid bilayer-associated components beyond the disclosure of cholera toxin subunit B (CTB) and ganglioside GM1.

This is simply incorrect, as evidenced by the page and line citations given in A2 above.

**A3.2** In response to a remark by Applicants that because the instant claims are to an assay method, it is nonsensical to request that Applicants must have described what lipid bilayer-associated component a test agent would bind to, the Examiner disagrees on the grounds that "at issue is whether all binding events would result in detectable changes in membrane fluidity" (page 10, Office action mailed May 3, 2007).

Applicants are unaware of a legal requirement that when claiming an assay method, e.g., a method for evaluating the presence or absence of an agent or analyte, it is required to show that all binding between a agent/analyte and a target is detectable.

The Examiner points to the Moran *et al.* article (page 7 of Office action mailed May 3, 2007) to support the position that not all binding events produce an effect on membrane fluidity. Indeed, this is not unexpected to one skilled in the art, and is exactly the reason that the claimed assay finds commercial use – to ascertain whether a test agent binds to a particular lipid target. It is generally known in the art that all assays have the potential for "false positives" and "false negatives" and there are numerous reports of viable assays with such "false positive" and/or "false negatives." The fact that false positives or false negatives occur, or even that no result occurs during an assay, does not give basis for a lack of written description.

In summary, Applicants submit that the application as originally filed provides sufficient information to convey to a skilled artisan that the inventors were in possession of the claimed assay method at the time of filing. Reversal of the rejection that the claims fail to comply with the written description requirement is respectfully requested.

**B. Enablement Rejection**

The enablement rejection is maintained on the grounds that a skilled artisan cannot make and use the assay method because the genus of test agents is of substantial variance, and it is unpredictable whether all possible test agents would have an effect on membrane fluidity.

**B1. The Legal Standard**

To satisfy the enablement requirement, a patent application must adequately disclose the claimed invention so as to enable a person skilled in the art to which the invention pertains to practice the invention at the time the application was filed without undue experimentation. *Enzo Biochem, Inc. v. Calgene, Inc.*, 52 USPQ2d 1129, 1136 (Fed. Cir. 1999).

**B2. Meeting the Legal Standard**

The claimed assay method includes *inter alia* the steps of "evaluating membrane fluidity...." And "detecting binding of the test agent to the lipid bilayer-associated component...". (The other steps in the claimed method do not appear to be at issue in the enablement rejection).

Evaluating membrane fluidity is known in the art and described in the specification page 14, line 19 through page 15, line 15. Example 6 in the application provides working details to conduct such tests. Detecting binding of the test agent to the lipid bilayer-associated component is immediately deduced based on whether a change in membrane fluidity occurred. Thus, these steps are not undue for a skilled artisan to accomplish, nor unpredictable in any way.

As a working example, Applicants direct the panel to Example 7 of the application, where the assay method is demonstrated using the test agent cholera toxin and its binding to ganglioside GM1. Applicants also direct the panel to the three journal articles noted by the Examiner on pages 7-8 of the May 3, 2007 Final Office action. These three articles each describe that compounds (i.e. test agents) can interact with lipid or membranes, and that a change in membrane fluidity may occur as a result of that interaction. This is further evidence that a skilled artisan can make and use the claimed assay method without undue experimentation. It does not matter that some test agents will not bind to a bilayer lipid associated component, since that is the point of the assay – to ascertain whether an interaction between two components occurs. If it does not occur, this is valuable information, for example, to know that that particular agent may not be therapeutically effective.

Accordingly, Applicants request reversal of the rejections, and a favorable decision on the allowability of the pending claims.

Respectfully submitted,  
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